

Figure 1A

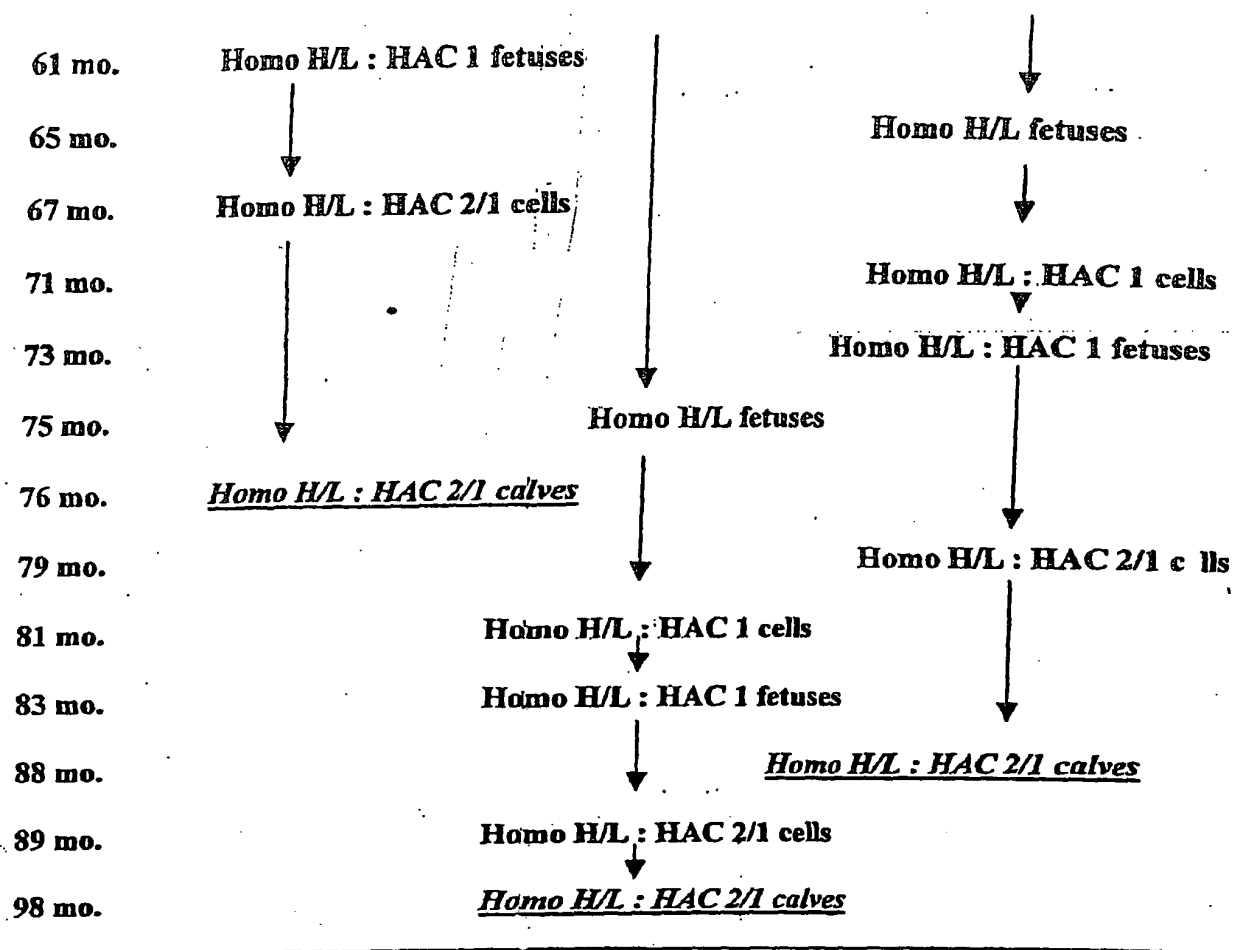


Figure 1A continued

FOI b7E b7C b7D

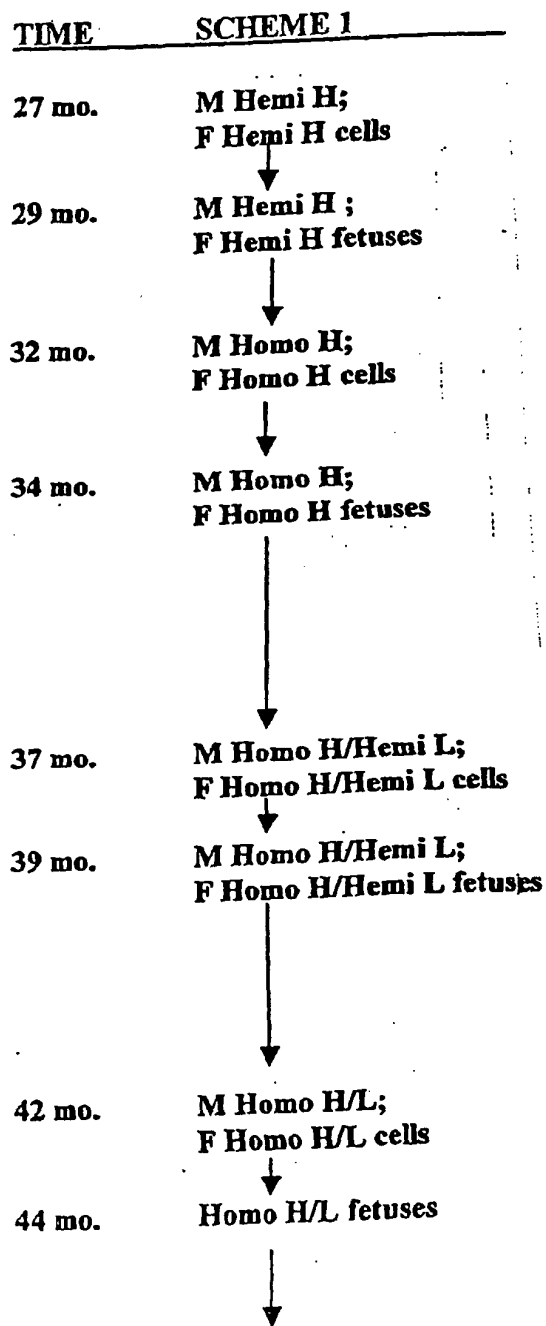


Figure 1B

47 mo. Homo H/L : Δ or $\Delta\Delta$ HAC cells

↓

49 m . Homo H/L : Δ or $\Delta\Delta$ HAC fet

↓

58 mo. Homo H/L; Δ or $\Delta\Delta$ HAC calf

098815-11601

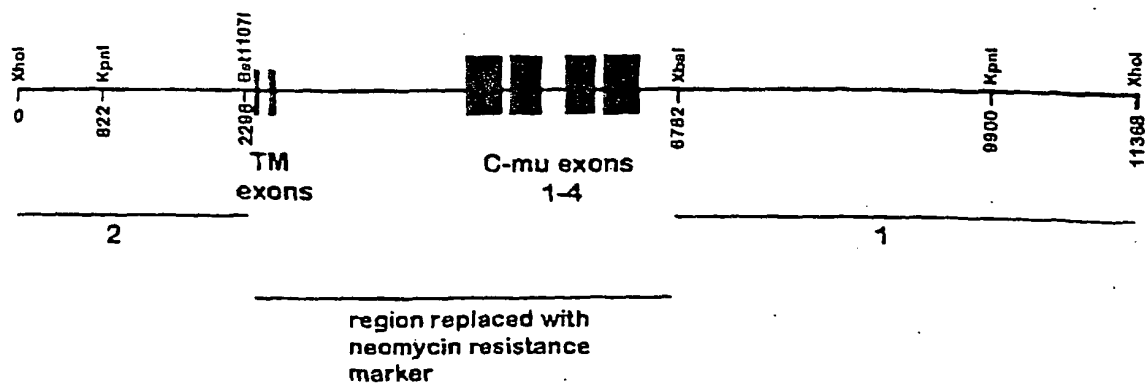


Figure 2A

0998345-14504

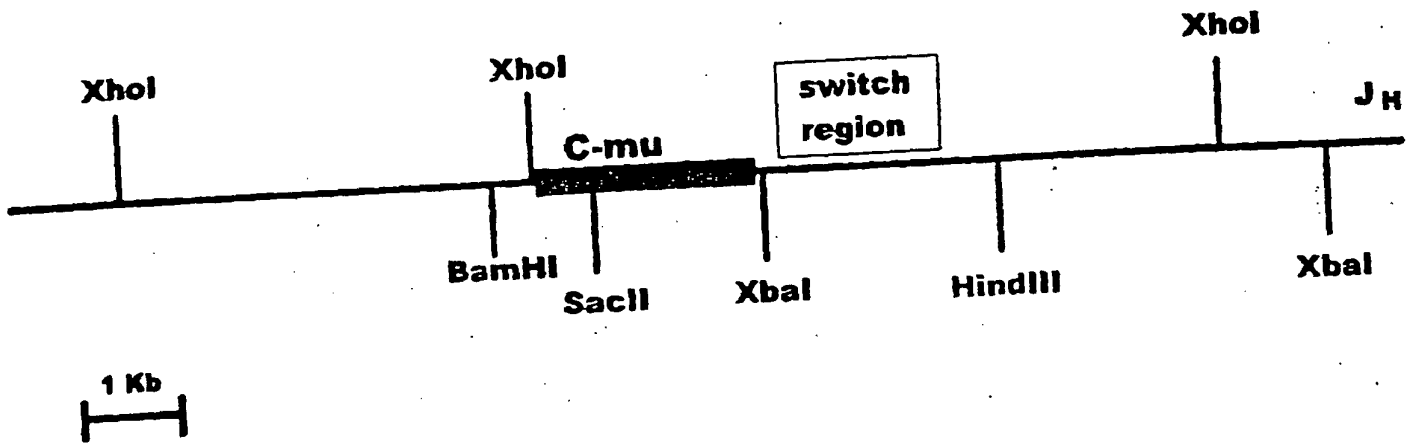
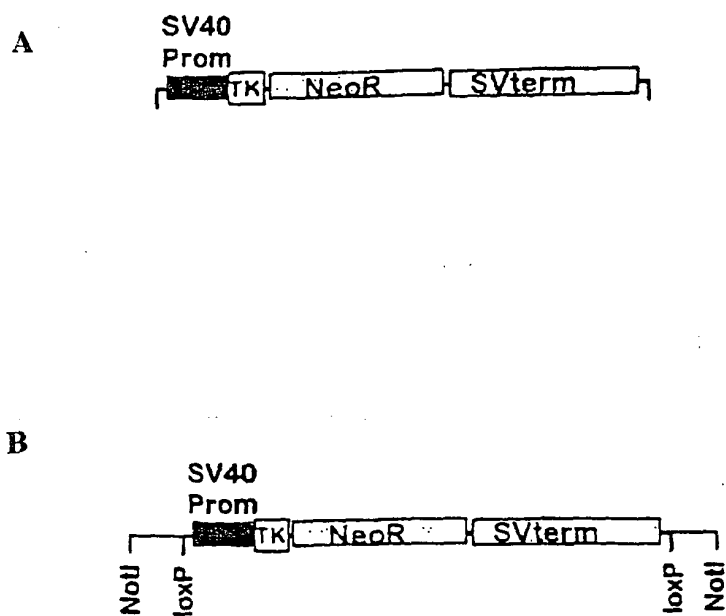


Figure 2B



Figures 3A and 3B

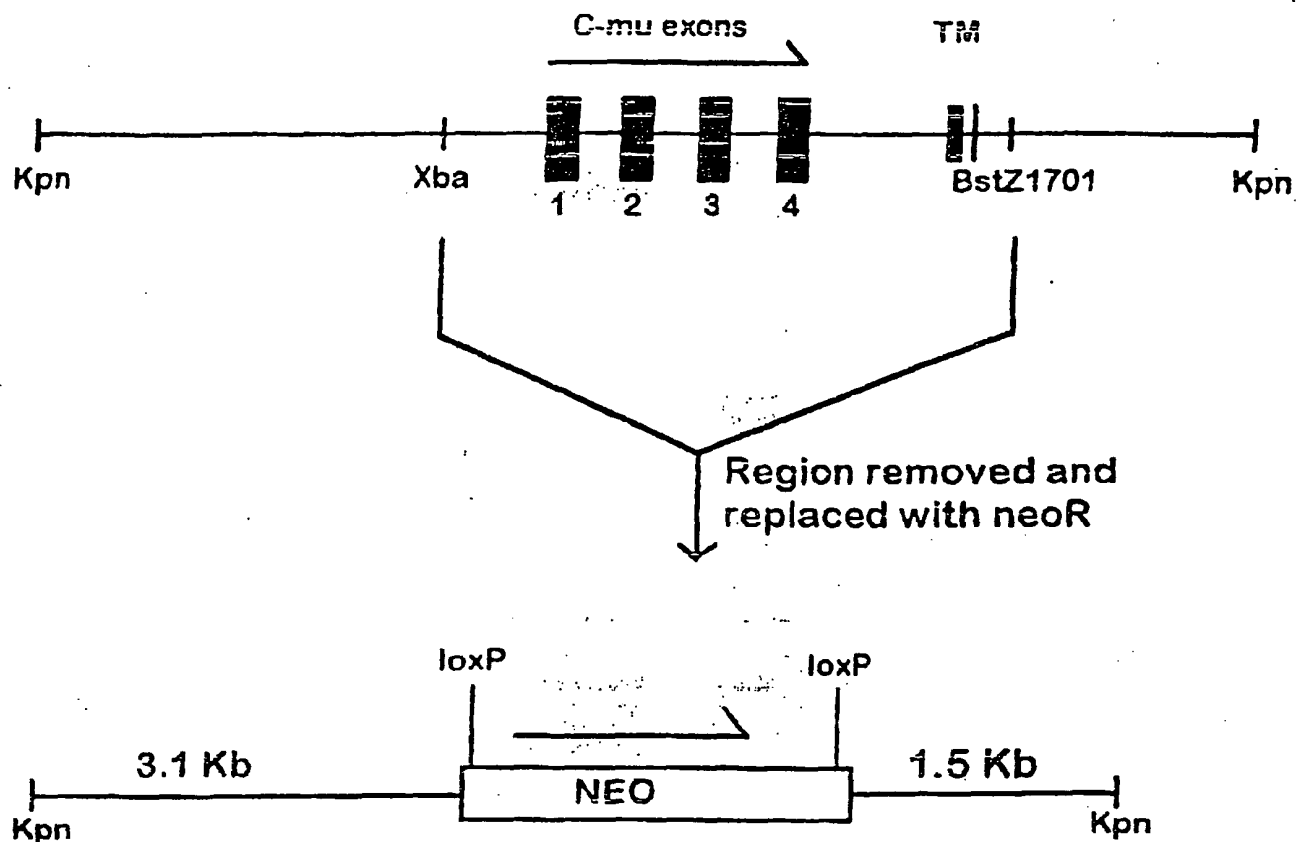


Figure 3C

SEQ ID NO: 47

ggtaccgaaaggcggccctgaacattctgcagtgagggagccgactgagaaagctgcttcacgccgggagggagccagc
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Figure 3D

0998115-111601

FOR THE

Figure 3E

090815-11601

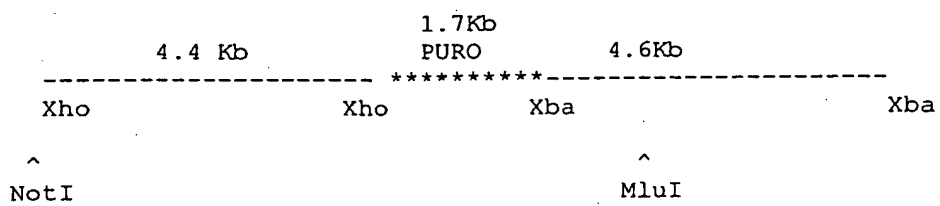


Figure 3F

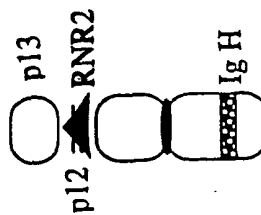
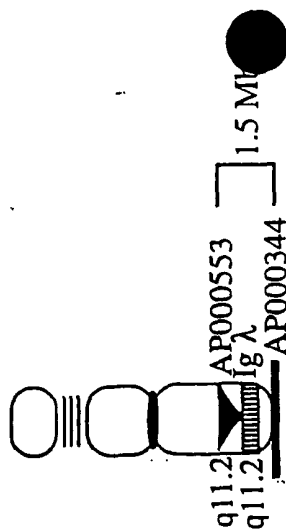
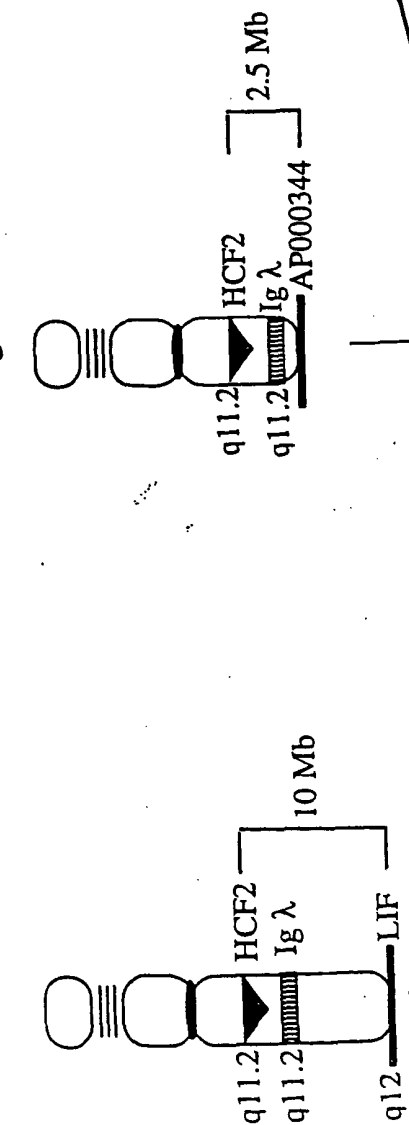
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1 atgagattcc ctgctcagct cctggggctc ctctgctct ggggtcccagg
 51 atccagtggg gatgttgtgc tgaccagac tcccctctcc ctgtctatca
 101 tccctggaga gacggctctcc atctcctgca agtctactca gagtctgaaa
 151 tatagtgatg gaaaaaccta tttgtactgg cttcaacata aaccaggcca
 201 atcaccacag cttttgatct atgctgtttc cagccgttac actgggggtcc
 251 cagacagggt cactggcagt gggtcagaaa cagatttcac acttacgac
 301 aacagtgtgc aggctgagga tgttggagtc tattactgtc ttcaaacaac
 351 atatgtcca aatactttcg gccaaaggac caaggtagag atcaaaaggt
 401 ctgatgctga gccatccgtc ttcctcttca aaccatctga tgagcagctg
 451 aagaccggaa ctgtctctgt cgtgtgcttg gtgaatgatt tctaccccaa
 501 agatatcaat gtcaagtgga aagtggatgg gggtactcag agcagcagca
 551 acttccaaaa cagtttcaca gaccaggaca gcaagaaaag cacctacagc
 601 ctcagcagca tcctgacact gccagctca gactaccaa gccatgacgc
 651 ctatacgtgt gaggtcagcc acaagagcct gactaccacc ctcgtaaga
 701 gcttcagtaa gaacgagtgt tag

Figure 3G

090815.1401

#22 fragments



#14 SC20

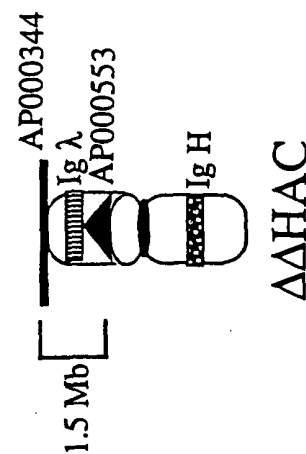
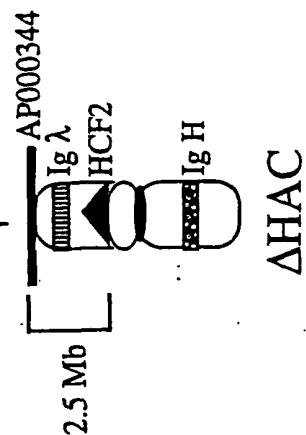
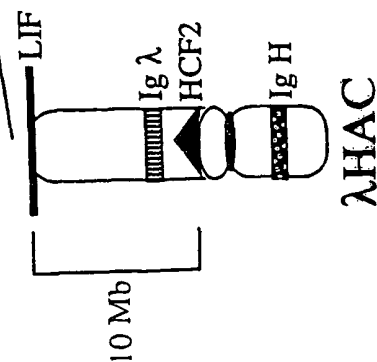
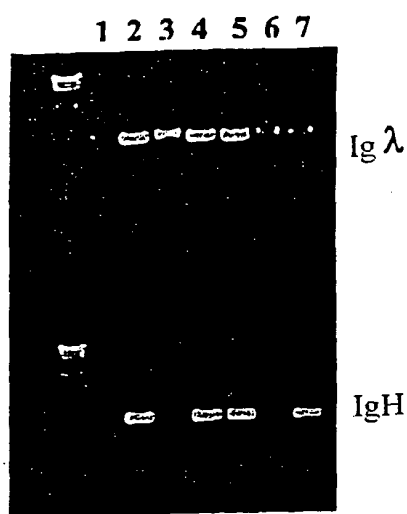


Figure 4

▲ ; loxP site
— ; telomere-truncation

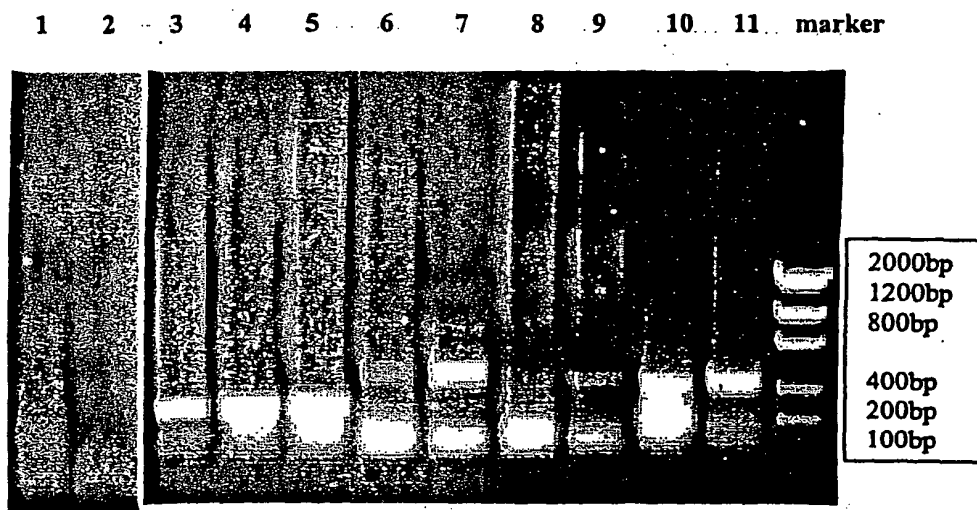
099845.4401



1. Bovine genomic DNA (negative control)
2. Fetus 5968 genomic DNA at 56 days
3. Fetus 5983 genomic DNA at 56 days
4. Fetus 6032 genomic DNA at 58 days
5. Fetus 6045 genomic DNA at 56 days
6. Fetus 5846 genomic DNA at 79 days
7. Fetus 5996 genomic DNA at 77 days

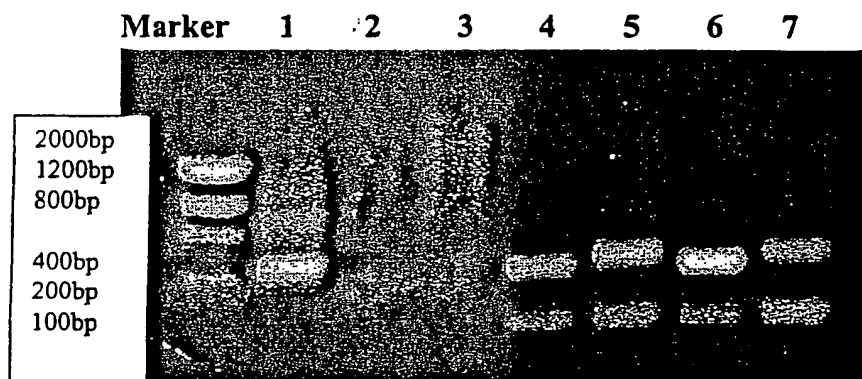
Fetus	Clone	IgH	Ig λ
5968	B4-2	Pos	Pos
5983	B2-13	Neg	Neg
6032	B4-8	Pos	Pos
6045	B2-22	Pos	Pos
5846	B4-8	Neg	Neg
5996	B4-2	Pos	Neg

Figure 5



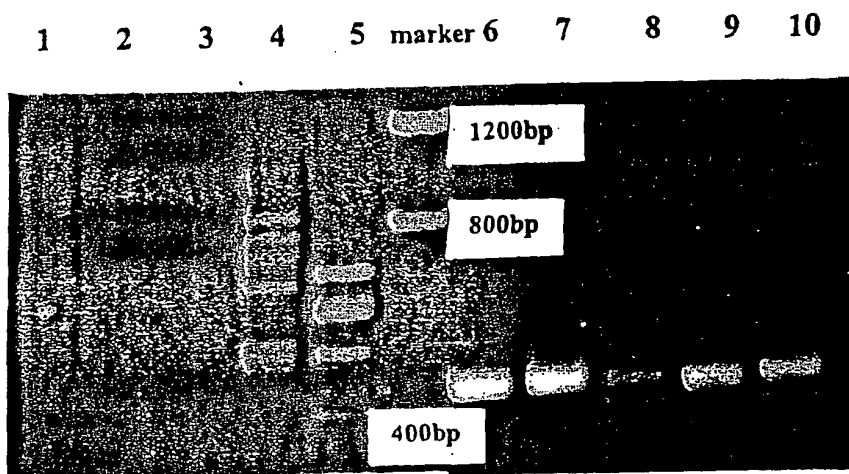
1. Human mu constant region in bovine liver cDNA from fetus 5996.
2. Human mu constant region in bovine brain cDNA from fetus 5996.
3. Human mu constant region in bovine spleen cDNA from fetus 5996.
4. Human mu constant region in human spleen cDNA.
5. Human mu constant region in mouse spleen CDNA with HAC.
6. Bovine rearranged Cmu heavy chain in bovine spleen cDNA from fetus 5996.
7. Bovine rearranged Cmu heavy chain in human spleen cDNA.
8. Bovine rearranged Cmu heavy chain in mouse spleen CDNA with HAC.
9. GAPDH primers in bovine spleen cDNA from fetus 5996.
10. GAPDH primers in bovine liver cDNA
11. GAPDH primers in mouse spleen CDNA with HAC.

Figure 6



1. GAPDH primers in bovine liver cDNA
2. Bovine rearranged Cmu heavy chain in bovine brain cDNA from fetus 5996.
3. Bovine rearranged Cmu heavy chain in bovine liver cDNA from fetus 5996.
4. GAPDH primers in bovine spleen cDNA from fetus 5996.
5. Bovine rearranged Cmu heavy chain in bovine spleen cDNA from fetus 5996.
6. GAPDH primers in in bovine brain cDNA from fetus 5996.
7. Bovine rearranged Cmu heavy chain positive control.

Figure 7



1. Human rearranged Cmu heavy chain in mouse spleen CDNA with HAC (+ control).
2. Human rearranged Cmu heavy chain in bovine liver cDNA from fetus.
3. Human rearranged Cmu heavy chain in bovine brain cDNA from fetus 5996
4. Human rearranged Cmu heavy chain in human spleen cDNA (+ control).
5. Human rearranged Cmu heavy chain in bovine spleen cDNA from fetus 5996.
6. GAPDH primers in bovine spleen cDNA from fetus 5996.
7. GAPDH primers in in mouse spleen CDNA with HAC
8. GAPDH primers in bovine brain cDNA from fetus 5996.
9. GAPDH primers in bovine liver cDNA from fetus 5996.
10. GAPDH primers positive control.

Figure 8

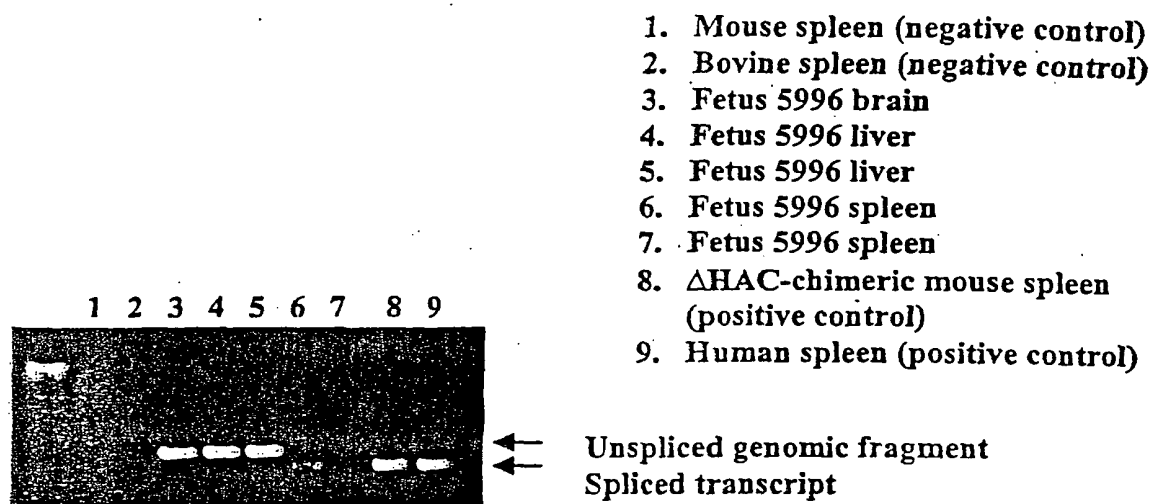
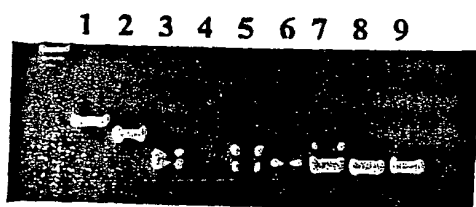


Figure 9

09988415-11501



1. Mouse spleen (negative control)
2. Bovine spleen (negative control)
3. Fetus 5996 brain
4. Fetus 5996 liver
5. Fetus 5996 liver
6. Fetus 5996 spleen
7. Fetus 5996 spleen
8. Δ HAC-chimeric mouse spleen (positive control)
9. Human spleen (positive control)

Figure 10

Figure 11A SEQ ID NO: 49

5'
GGGAAGGAAGTCCTGTGCGGACCANCCAACGGGCACGGCTGCTCGTATCCGACG
GGGAATTCTCACAGGAGACGAGGGGGGAAAAGGGTTGGGGCGGATGCACCTCC
CTGACGAGACGGTGACGACGGGTTCGNTGGCCCCCAGNNGTCAAA3'

Figure 11B SEQ ID NOs: 50 and 51

V-D-J region | → constant mu region

Subject: 5'
tttgactactggggccaggggaaccctggtcaccgtctcctcagggagtgcacccgccccca
-----nn-----n-----
Query

Subject:
acccttttccccctcgtctcctgtgagaattccccgtcggatacagagcagcgtggccggtt

Query

Subject: 5'
ggctgcctcgcacaggacttccttccccgactccatcacttctccctg 3'
--n--g----- Cmul primer

090316-1604
TTTTT

SEQ ID NOs 52 and 53

10 19 28 37 46 55
 5' GGA GGC TTG GTC AAG CCT GGA GGG TCC CTG AGA CTC TCC TGT GCA GCC TCT GGA
 G G L V K P G G S L R L S C A A S G

64 73 82 91 100 109
 TTC ACC TTC AGT GAC TAC TAC ATG AGC TGG ATC CGC CAG GCT CCA GGG AAG GGG
 F T F S D Y Y M S W I R Q A P G K G

118 127 136 145 154 163
 CTG GAG TGG GTT TCA TAC ATT AGT AGT AGT GGT AGT ACC ATA TAC TAC GCA GAC
 L E W V S Y I S S S G S T I Y Y A D

VH3-11
 172 181 190 199 208 217
 TCT GTG AAG GGC CGA TTC ACC ATC TCC AGG GAC AAC GCC AAG AAC TCA CTG TAT
 S V K G R F T I S R D N A K N S L Y

226 235 244 253 262 271
 CTG CAA ATG AAC AGC CTG AGA GCC GAG GAC ACG GCT GTG TAT TAC TGT GCG AGA
 L Q M N S L R A E D T A V Y Y C A R

280 289 298 307 316 325
 ATA ACT GGG GAT GCT TTT GAT ATC TGG GGC CAA GGG ACA ATG GTC ACC GTC TCT
 I T G D A F D I W G Q G T M V T V S

D7-27 JH3
 334 343 352 361 370 379
 TCA GGG AGT GCA TCC GCC CCA ACC CTT TTC CCC CTC GTC TCC TGT GAG AAT TCC
 S G S A S A P T L F P L V S C E N S

388
 CCG TCG GAT ACG AGC 3'
 P S D T S

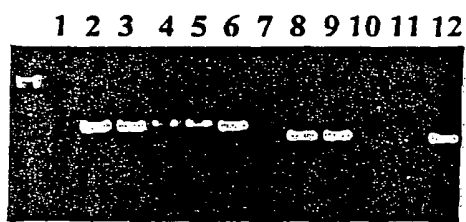
098815.1601

Figure 12A

SEQ ID NOs: 54 and 55

5' GTG GAG TCT GGG GGA GGC TTG GTA CAG CCT GGG AGG TCC CTG AGA CTC TCC TGT
V E S G G G L V Q P G R S L R L S C
GCA GCG TCA GGA TTC ACC TTC AGG AAC TTT GGC ATG CAC TGG GTC CGC CAG GCT
A A S G F T F R N F G M H W V R Q A
VH3-33
CCA GGC AAG GGG CTG GAG TGG GTG ACA GTT ATA TGG TAT GAC GGA AGT AAT CAA
P G K G L E W V T V I W Y D G S N Q
TAC TAT ATA GAC TCC GTG AAG GGC CGA TTC ACC ATC TCC AGA GAC AAT TCC AAG
Y Y I D S V K G R F T I S R D N S K
AAC ATG TTG TAT CTG CAA ATG AAC AGC CTG AGA GCC GAG GAT ACG GCT GTG TAT
N M L Y L Q M N S L R A E D T A V Y
TAC TGT GCG AGA GAT CGC AAT GGC CTG AAG TAC TTC GAT CTC TGG GGC CGT GGC
Y C A R D R N G L K Y F D L W G R G
D6-19? N addition JH2
ACC CTG GTC ACT GTC TCA TCA GGG AGT GCA TCC GCC CCA ACC CTT TTT CTT CTT
T L V T V S S G S A S A P T L F P L
Gn
GTC TCC TGT GAG AAT TCC CCG TCG GAT ACG AGC 3'
V S C E N S P S D T S

Figure 12B

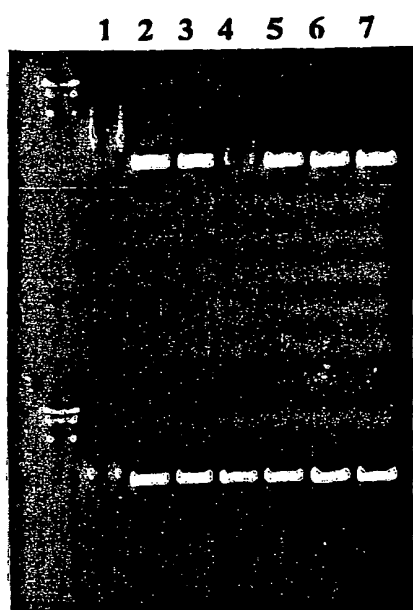


Fetus	Clone	IgH	Igλ
5580	412	Pos	Pos
5848	214	Neg	Neg

1. Bovine genomic DNA (negative control)
2. Fetus 5580 genomic DNA (Igλ)
3. Fetus 5580 genomic DNA (Igλ)
4. Fetus 5848 genomic DNA (Igλ)
5. Fetus 5848 genomic DNA (Igλ)
6. Positive control (Human genomic DNA)
7. Bovine genomic DNA (negative control)
8. Fetus 5580 genomic DNA (IgH)
9. Fetus 5580 genomic DNA (IgH)
10. Fetus 5848 genomic DNA (IgH)
11. Fetus 5848 genomic DNA (IgH)
12. Positive control (Human genomic DNA)

Figure 13

0998815.144501



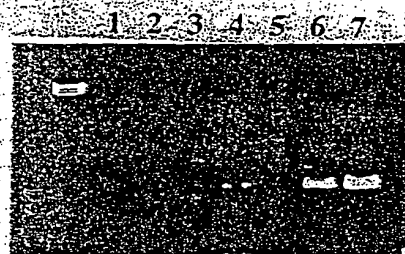
IgH

1. Bovine genomic DNA (negative control)
2. Fetus 5442A genomic DNA (9¹ day)
3. Fetus 5442A genomic DNA (9¹ day)
4. Fetus 5442B genomic DNA (9¹ day)
5. Fetus 5442B genomic DNA (9¹ day)
6. Fetus 5968 genomic DNA (56 day; positive control)
7. Human genomic DNA (positive control)

Igλ

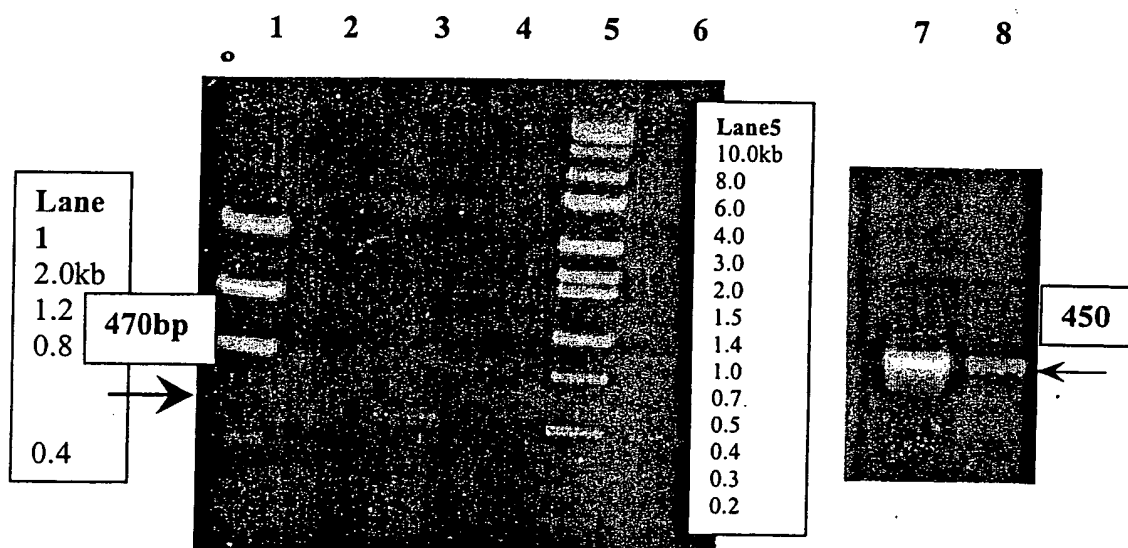
Figure 14

- [illegible]



Unspliced genomic fragment
Spliced transcript

Figure 15



1. Low Mass Ladder: 2.0, 1.2, 0.8, 0.4, 0.2 and 0.1kb
2. Normal Bovine spleen cDNA negative control
3. $\Delta\Delta$ HAC 5868A spleen cDNA
4. empty
5. Hi Lo
:10.0,6.0,4.0,3.0,2.0,1.5,1.4,1.0,0.7,0.5,0.4,0.3, 0.2,0.1kb
6. Tc Mouse HAC spleen cDNA positive control
7. GAPDH product from 5868A spleen cDNA
8. GAPDH product from normal bovine spleen cDNA

Figure 16

0998815 11501

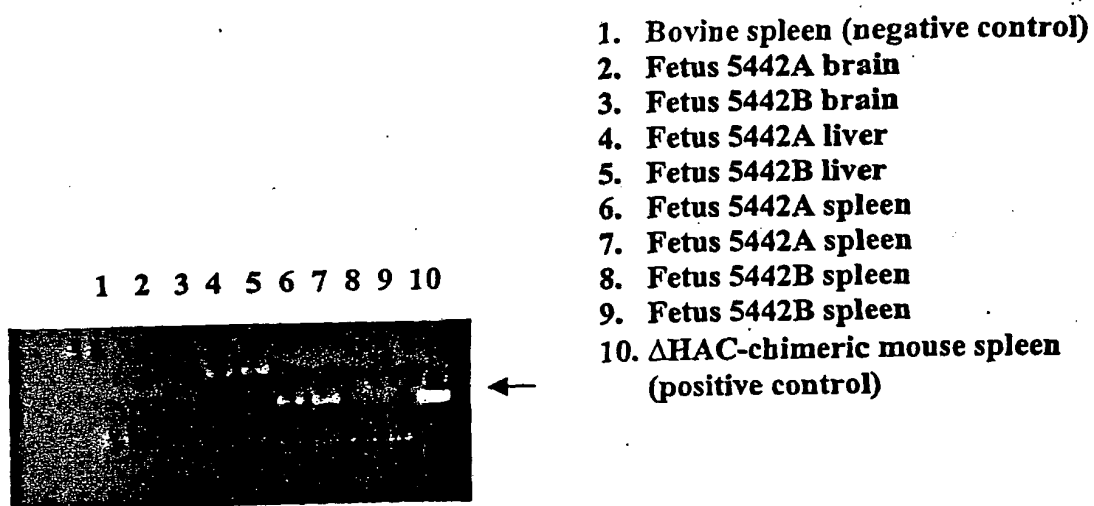
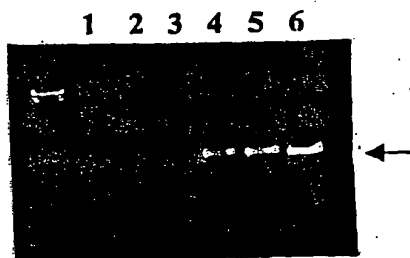


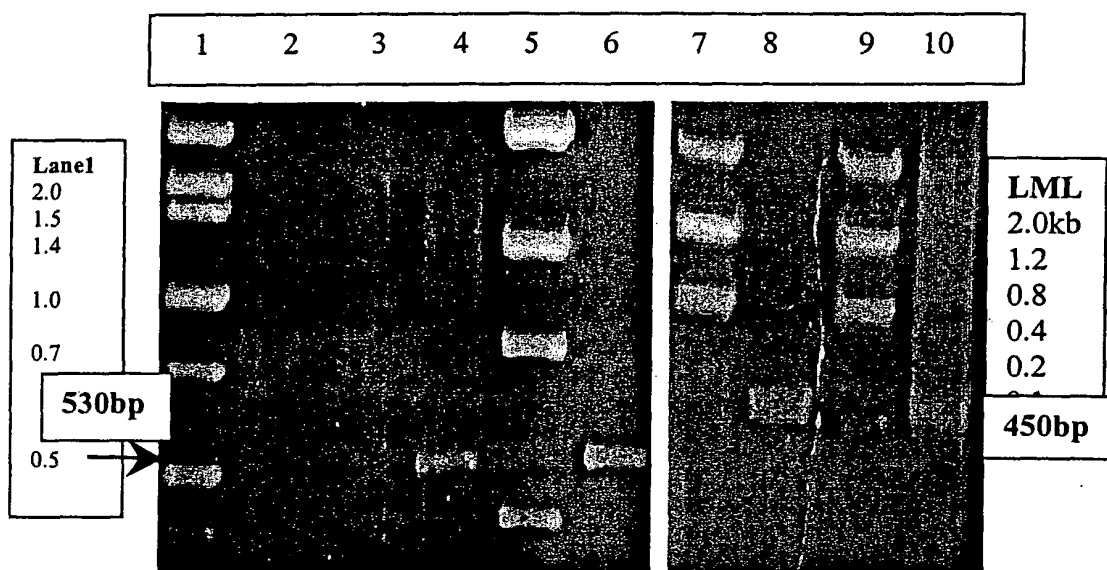
Figure 17

099815-1404
T09T5T866



1. Bovine spleen (negative control)
2. Fetus 5442A brain
3. Fetus 5442A liver
4. Fetus 5442A spleen
5. Fetus 5442A spleen
6. Δ HAC-chimeric mouse spleen (positive control)

Figure 18



1. Hi-Lo MW:2.0,1.5,1.4,1.0,0.7,0.5 kb
2. ΔΔHAC 5868A fetal brain cDNA
3. ΔΔHAC 5868A fetal liver cDNA
4. ΔΔHAC 5868A fetal spleen cDNA
5. Low Mass Ladder
6. Tc Mouse HAC spleen cDNA positive control (530bp)
7. Low Mass Ladder
8. GAPDH ΔΔHAC 5868A brain cDNA
9. Low Mass Ladder
10. GAPDH ΔΔHAC 5868A liver cDNA

Figure 19

SEQ ID Nos: 56 and 57

5' ACC CTC CTC ACT CAC TGT GCA GGG TCC TGG GCC CAG TCT GTG CTG ACT CAG CCA
T L L T H C A G S W A Q S V L T Q P

CCC TCA GCG TCT GGG ACC CCC GGG CAG AGG GTC ACC ATC TCT TGT TCT GGA AGC
P S A S G T P G Q R V T I S C S G S

AGC TCC AAC ATC GGA AGT AAT TAT GTA TAC TGG TAC CAG CAG CTC CCA GGA ACG
S S N I G S N Y V Y W Y Q Q L P G T

GCC CCC AAA CTC CTC ATC TAT AGG AAT AAT CAG CGG CCC TCA GGG GTC CCT GAC
A P K L L I Y R N N Q R P S G V P D

Y1-17

CGA TTC TCT GGC TCC AAG TCT GGC ACC TCA GCC TCC CTG GCC ATC AGT GGG CTC
R F S G S K S G T S A S L A I S G L

CGG TCC GAG GAT GAG GCT GAT TAT TACT GTG GCA TGG GAT GAC AGC CTG AGT
R S E D E A D Y Y C A A W D D S L S

GGT CTT TTC GGC GGA GGG ACC AAG CTG ACC GTC CTA GGT CAG CCC AAG GCT GCC
G L F G G G T K L T V L G Q P K A A

JL3

CCC TCG GTC ACT CTG TTC CCA CCC TCC TCT GAG GAG CTT CAA GCC AAC AAG GCC
P S V T L F P P S S E E L Q A N K A

CA

ACA CTG GTG 3'
T L V

SEQ ID NOs: 58 and 59

5' AGT TGG ACC CCT CTC TGG CTC ACT CTC TTC ACT CTT TGC ATA GGT TCT
S W T P L W L T L F T L C I G S

GTG GTT TCT TCT GAG CTG ACT CAG GAC CCT GCT GTG TCT GTG GCC TTG GGA CAG
V V S S E L T Q D P A V S V A L G Q

ACA GTC AGG ATC ACA TGC CAA GGA GAC AGC CTC AGA AGC TAT TAT GCA AGC TGG
T V R I T C Q G D S L R S Y Y A S W

TAC CAG CAG AAG CCA GGA CAG GCC CCT GTA CTT GTC ATC TAT GGT AAA AAC AAC
Y Q Q K P G Q A P V L V I Y G K N N V2-13

CGG CCC TCA GGG ATC CCA GAC CGA TTC TCT GGC TCC AGC TCA GGA AAC ACA GCT
R P S G I P D R F S G S S G N T A

TCC TTG ACC ATC ACT GGG GCT CAG GCG GAA GAT GAG GCT GAC TAT TAC TGT AAC
S L T I T G A Q A E D E A D Y Y C N

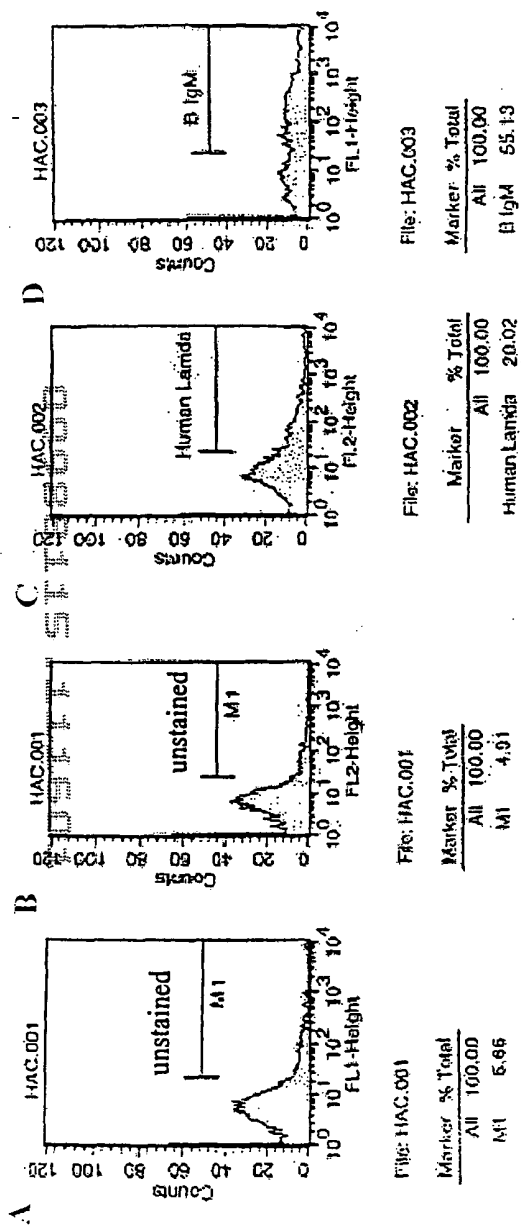
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S R D S S G N H L V F G G G T K L T JL2

GTC CTA GGT CAG CCC AAG GCT GCC CCC TCG GTC ACT CTG TTC CCA CCC TCC TCT
V L G Q P K A A P S V T L F P P S S

GAG GAG CTT CAA GCC AAC AAG GCC ACA CTG GTG 3'
E E L Q A N K A T L V

CA

Fetus #5442A



Fetus #5442B

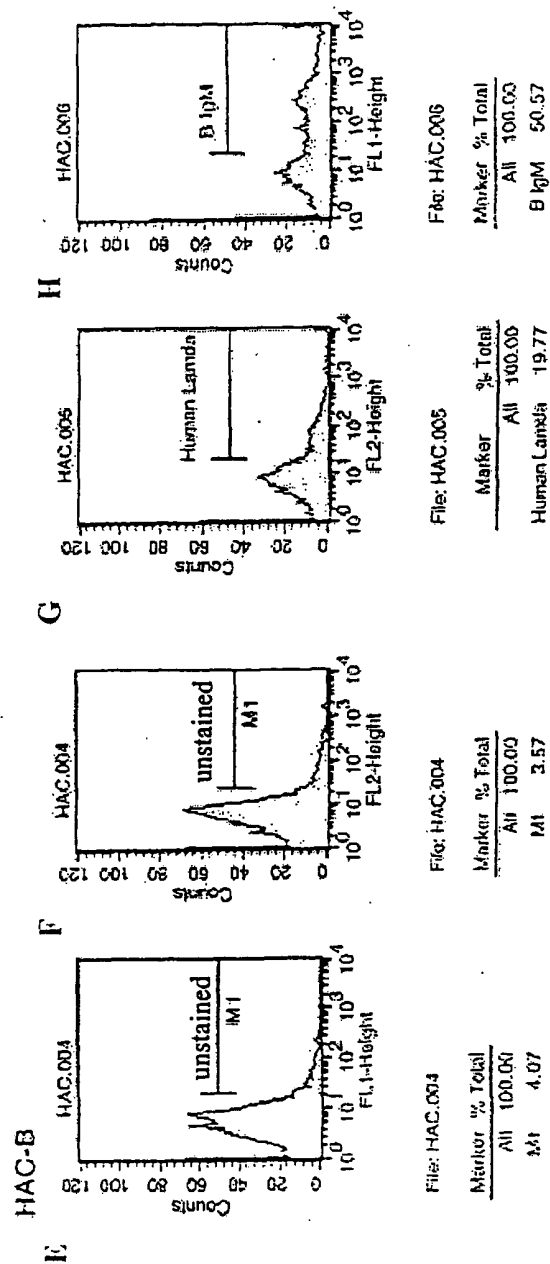


Figure 22A - 22H

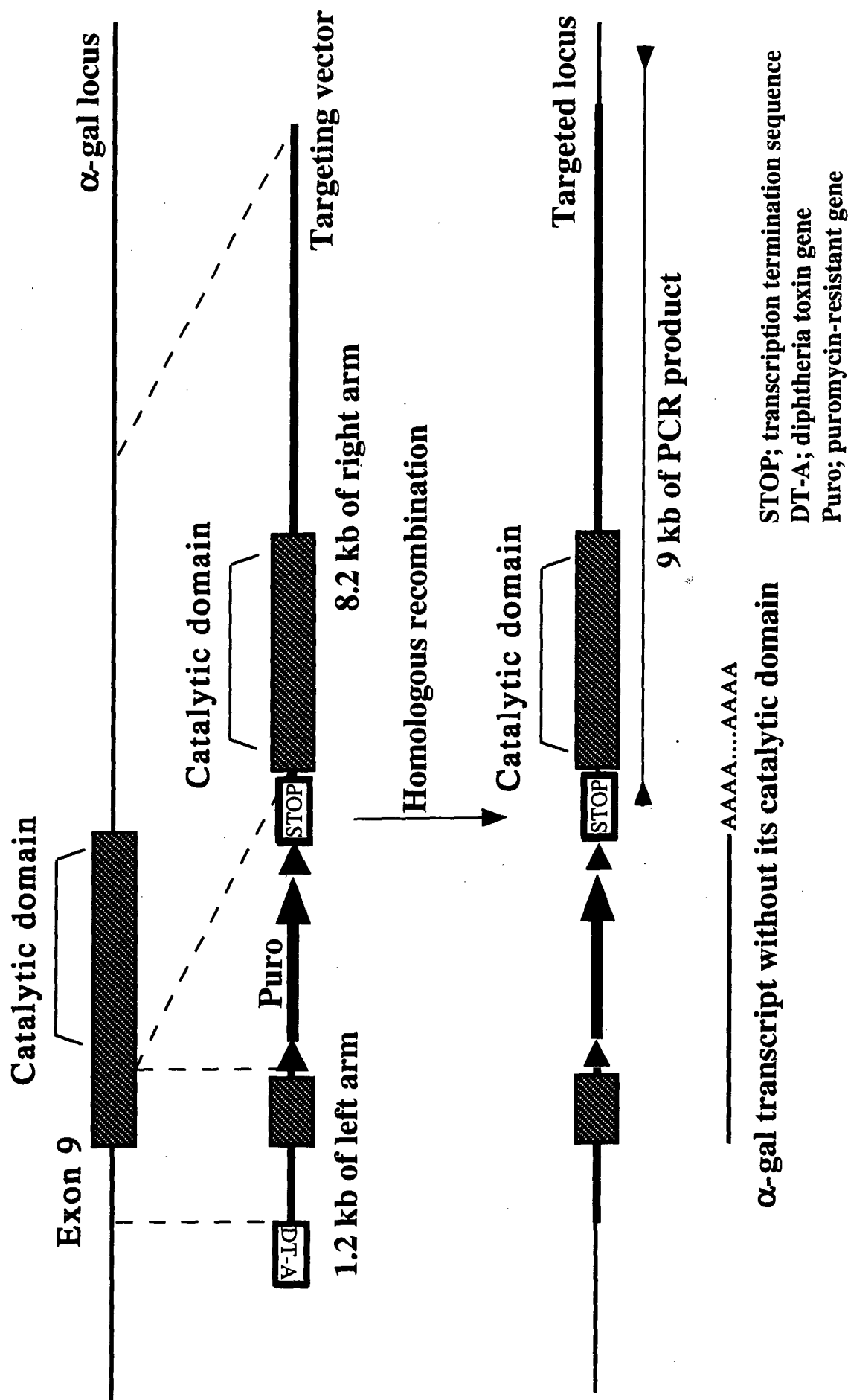
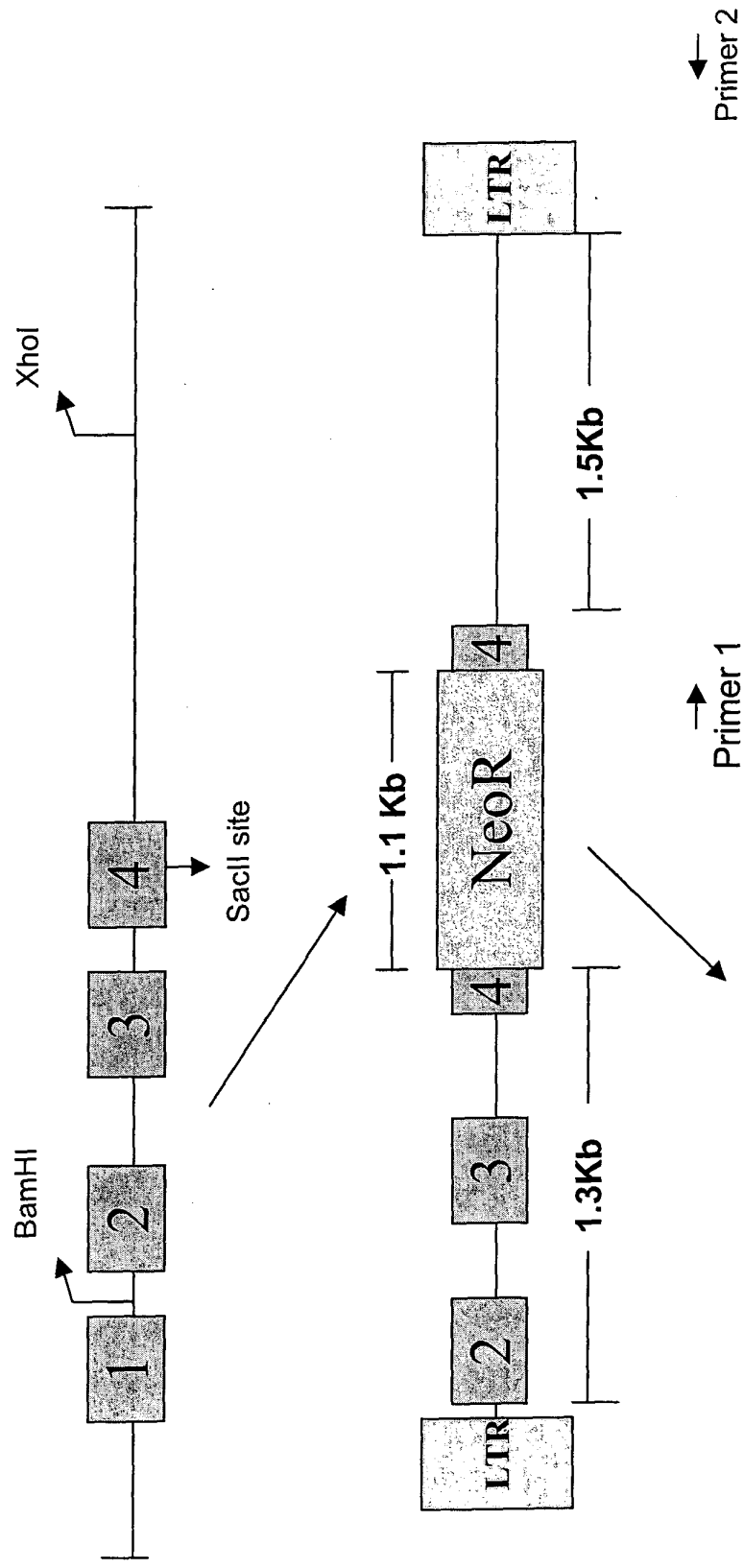


Figure 23



PACKAGE AAV PARTICLES

Figure 24

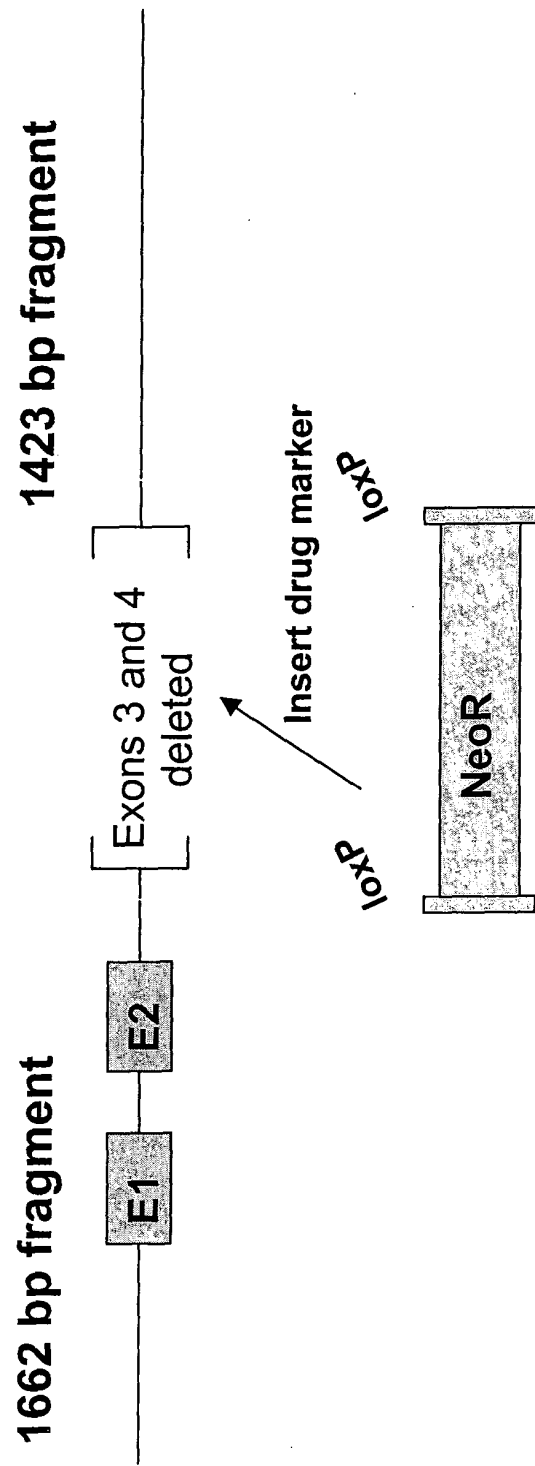


Figure 25

FOSTT" 5TF88660

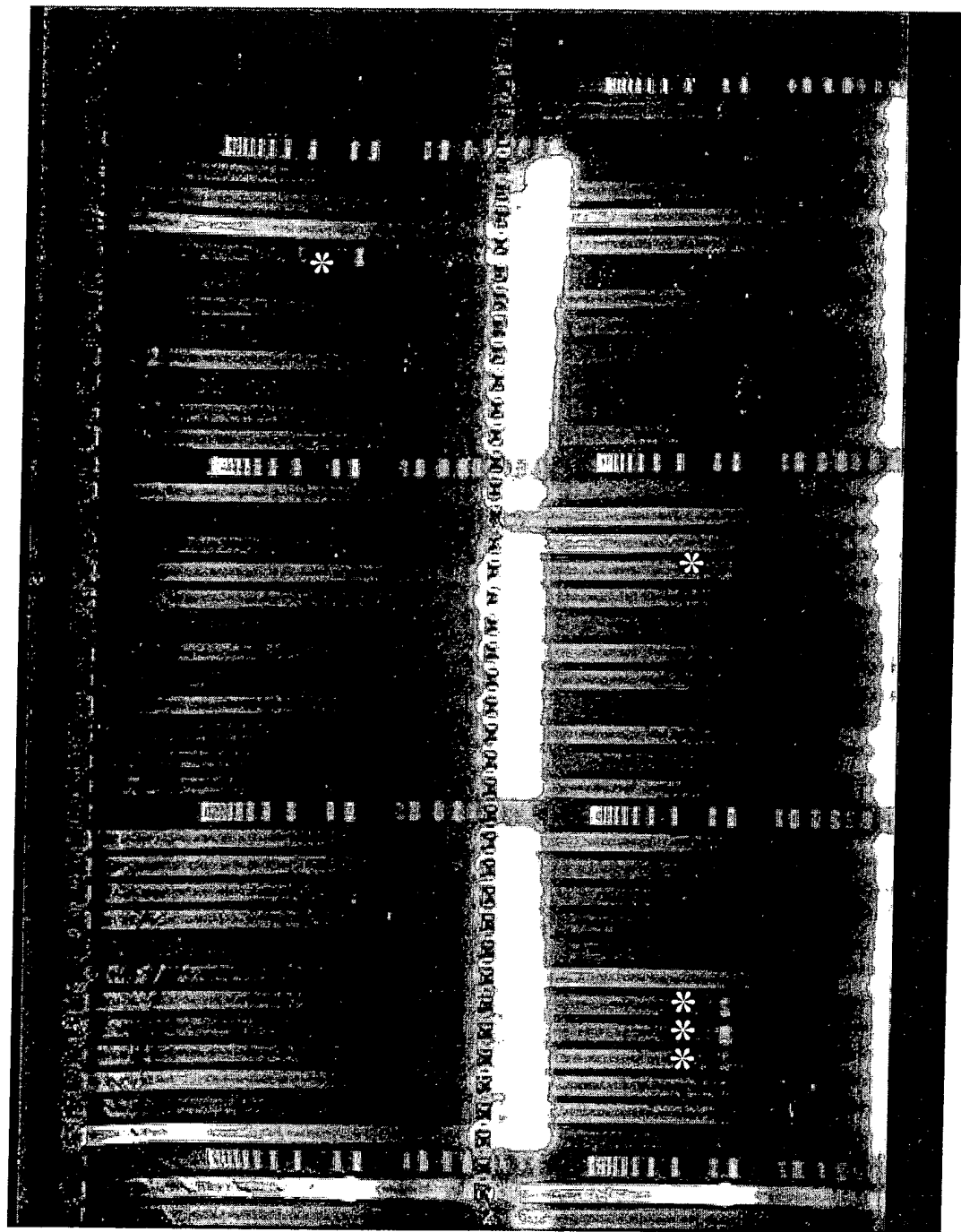


Figure 26

NT, ET and pregnancies: Delta HAC regenerated fibroblasts

Cell line ID	Total NTs in culture	No of Blast (%)	No of Blast Transferred	No Recips	Pregnancy status							
					40 d	60 d	90 d	120 d	150 d	180 d	210 d	
D5968	174	34 (28)	27	17	3	3	3	3	3	3	3	3
D6045	215	10 (7)	8	4	1	1	1	1	1	1	1	1
D6045	122	20 (23)	12	9	1	0	0	0	0	0	0	0
D6032	161	18 (16)	14	7	3	3	3	3	2	2	2	2
D6032	188	15 (11)	11	11	3	0	0	0	0	0	0	0
D6032	198	20 (14)	16	10	1	1	1	1	1	1	1	1
D6032	200	17 (12)	12	8	2	2	2	2	2	2	2	2
D6032	180	11 (9)	10	5	3	1	1	1	0	0	0	0
D6032	135	22 (23)	22	11	2	2	1	1	1	1	1	1
D5968	140	35 (36)	25	13	2	2	2	2	1	1	1	1
D5968	180	30 (24)	26	13	2	2	2	2	2	2	2	2
D6045	170	46 (39)	32	16	4	4	4	4	4	4	4	4
D6045	80	7 (13)	1	1	0	0	0	0	0	0	0	0
D6045 SLOT	108	9 (12)	3	2	1	1	1	1	1	1	1	1
D6045	76	8 (15)	2	2	0	0	0	0	0	0	0	0
D6045 SLOT	128	12 (13)	7	5	0	0	0	0	0	0	0	0
D6045	47	6 (18)	5	3	2	2	2	2	2	2	2	2
D6045 SLOT	112	3 (4)	3	2	2	2	2	2	2	2	2	2
D6045	120	28 (33)	18	9	18	9	18	9	18	9	18	9
D6045 SLOT	100	11 (16)	2	1	11	16	2	1	11	16	2	1
D6045	78	15 (27)	16	8	15	27	16	8	15	27	16	8
D6045 SLOT	91	0	2	1	2	1	2	1	2	1	2	1
D6045	98	16 (23)	10	5	16	23	10	5	16	23	10	5
D6045 SLOT	104	16 (22)	10	5	16	22	10	5	16	22	10	5
D5968	128	24 (27)	8	4	24	27	8	4	24	27	8	4
D5968 SLOT	65	10 (22)	8	4	10	22	8	4	10	22	8	4
D5968	120	28 (33)	14	7	28	33	14	7	28	33	14	7
D5968 SLOT	95	13 (19)	6	3	13	19	6	3	13	19	6	3
D5968	98	17 (25)	20	10	17	25	20	10	17	25	20	10
D5968 SLOT	93	14 (22)	12	6	14	22	12	6	14	22	12	6
D	13	1 (11)	1	3	1	11	1	3	1	11	1	3
SLOT	63	8 (18)	8	3	8	18	8	3	8	18	8	3
D	108	4 (5)	4	3	4	5	4	3	4	5	4	3
SLOT	100	1 (1)	1	3	1	1	1	3	1	1	1	3
D	90	10 (16)	10	6	10	16	10	6	10	16	10	6
SLOT	110	13 (17)	13	6	13	17	13	6	13	17	13	6
D	90	10 (16)	10	1	10	16	10	1	10	16	10	1
SLOT	83	5 (9)	5	1	5	9	5	1	5	9	5	1
D	105	20 (27)	20	9	20	27	20	9	20	27	20	9
SLOT	78	7 (13)	7	2	7	13	7	2	7	13	7	2
D	88	7 (11)	7	4	7	11	7	4	7	11	7	4
SLOT	93	9 (14)	9	4	9	14	9	4	9	14	9	4
D	85	20 (33)	20	10	20	33	20	10	20	33	20	10
SLOT	77	4 (7)	4	2	4	7	4	2	4	7	4	2
	4987	515 (19)	481	258								

Summary	Preg Status	No of Pregnancies
> 40 d		9
> 80 d		2
> 120 d		4
> 180 d		3
> 210 d		3
Total		21